A new route for the convenient synthesis of 3-aminomethyl-3,5,5-trimethyl-cyclohexanol

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There has been considerable chemical and biological interest in influenza fusion inhibitors namely, 3-aminomethyl-3,5,5-trimethyl-cyclohexanol 5. This compound has been identified as an important inhibitor of influenza virus fusion derivative and a potent and effective surrogate for the quinolizidine moiety. A new convenient route for the synthesis of 5 and for two new intermediates 1,3,3-trimethyl-5-oxo-cyclohexane-carboxylic acid amide 3 and 5-hydroxy-1,3,3-trimethyl-cyclohexane-carboxylic acid amide 4.

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3-Aminomethyl-3,5,5-trimethyl-cyclohexanol was identified from parallel synthesis methodology as a potent inhibitors of influenza virus fusion and effective surrogate for the quinolizidine moiety. Consequently, amine 5 was used as the vehicle in the secondary library designed to complete the SAR survey by probing the effects of variation of the carboxylic acid element. To the amine end of 5 Deshpande et al.1 have coupled 200 structurally diverse carboxylic acids to give different quinolizidine inhibitors of influenza virus. The anti-influenza activity2 of thio-benzamide fusion inhibitors derived from 5 is well-known. Axial disposition of the thio amide moiety is essential for the potent influenza inhibitory activity. The synthesis of 5 was reported with different routes3. Previously reported synthetic routes gave low yield of 5. In the present synthetic method, the yield of 5 was 92%.

The synthetic sequence leading to the formation of compound 5 is depicted in the Scheme I. In one of the earlier reported routes, the isophorone 1 (3,5,5-trimethyl-cyclohex-2-enone) was subjected to nitrile addition by dissolving it in methanol, water, glacial acetic acid and then adding sodium cyanide solution and keeping it for one week to get the product after distillation. In one of the other method isophorone was suspended in aqueous sodium bisulfite solution and it was dissolved on heating and then sodium cyanide solution was added to it. Reaction mixture was put under reflux. After work-up less than 50% of product was obtained4. In another route KCN-NH4Cl-enone (2:1.5:1) in DMF was used5-6. In order to avoid side reaction, cyanation of 1 was carried out with two mole equivalents of potassium cyanide and 1.5 mole equivalents ammonium chloride7 in DMF-H2O. As the excess ammonium hydroxide was liberated as

![Scheme I](image-url)

Scheme I—(a) KCN, NH4Cl/DMF-H2O, 80°C, 16 hr (b) KOH, Et3O-H2O, 60°C, 18 hr (c) NaCNBH3, CH3CN, CH3COOH, 80°C, 18 hr (d) LiAlH4, THF, reflux, 24 hr
ammonia by heating (80°C for 16 hr), the reaction mixture was maintained at minimal basicity.

The compound 2 was treated with 10% KOH in EtOH-H2O (3:1) to give the amide 3. The ring carbonyl group in 3 was selectively reduced by sodium cyanoborohydride to give 4 (ref. 9), which was reduced with LiAlH4 to give 5 (ref. 8).

The easy availability of starting material and high yield of intermediates and the final product are the important features of the present synthetic route and worth reporting. The structural assignments of the products were based on their IR, EIMS and NMR spectra.

**Experimental Section**

**General.** Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin Elmer 399B spectrometer (v_{max} in cm⁻¹); ¹H and ¹³C NMR spectra on a Bruker 400 MHz spectrometer in CDCl₃ and DMSO-d₆ (chemical shifts in δ, ppm) with TMS as internal standard; and EIMS were scanned at 70 eV on a JNM-DX-300 spectrometer. Silica gel 230-400 mesh (Merck) was used for column chromatography and silica gel G for TLC. The spots were visualized by exposure to I₂ vapours and/or by spraying with ninhydrin solution followed by heating at 100°C for a few minutes. The required starting compound was purchased from Aldrich.

**1,3,3-Trimethyl-5-oxo-cyclohexane-carboxylic acid amide 3.** A solution of compound 2 (10 g, 60.52 mmoles) in 10% KOH in EtOH-H2O (3:1) (1500 mL) was stirred at 60°C for 18 hr and then poured into water and the resulting aqueous solution was acidified with 5% HCl and extracted with dichloromethane (3×350 mL). The organic phase was dried and recrystallised from diethyl ether to give the white crystalline solid 3, yield 87.9% (9.65 g); IR: 2960, 1716 (for amide carbonyl), 1666, 1466, 1368, 1285 cm⁻¹; EIMS m/z (rel. int.): 183 [M⁺] (26); ¹H NMR (400 MHz, CDCl₃): δ 0.98 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 1.34 (s, 3H, CH₃), 2.08 (m, 2H, CH₂), 2.68 (m, 2H, CH₂), 3.06 (m, 2H, CH₂); ¹³C NMR (100 MHz, CDCl₃): δ 21.0 (q), 23.02 (q), 28.64 (q), 32.24 (s), 34.9 (s), 48.4 (t), 52.8 (t), 58.7 (t), 186.2 (s), 206.2 (s). Anal. Found: C, 64.96; H, 9.12; N, 7.98. Calc. for C₁₀H₁₃NO₂: C, 65.54; H, 9.35; N, 7.64%.

**5-Hydroxy-1,3,3-trimethyl-cyclohexane-carboxylic acid amide 4.** Compound 3 (9 g, 49.11 mmoles) was dissolved in a mixture of acetonitrile (250 mL) and acetic acid (75 mL) and stirred for 18 hr with sodium cyanoborohydride (6.19 g, 98.23 mmoles) at 80°C. The solvents were evaporated in vacuo, the residue was treated with 15 N NaOH and extracted with four portions of ethyl acetate. Drying over Na₂SO₄ and evaporation of solvents yielded 4 as yellowish solid, yield 72% (6.55 g); IR: 3355 (for OH), 2958, 1707 (for amide carbonyl), 1606, 1542, 1466, 1368, 1285 cm⁻¹; EIMS m/z (rel. int.): 185 [M⁺] (20); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (s, 3H, CH₃), 1.05 (s, 3H, CH₃), 1.30 (s, 3H, CH₃), 1.54 (d, J=1.6 Hz, 1H), 2.15 (m, 2H), 2.28 (m, 3H), 2.65 (m, 1H, CH-OH); ¹³C NMR (100 MHz, DMSO-d₆): δ 21.0 (q), 23.32 (q), 27.85 (q), 32.18 (s), 37.85 (s), 43.46 (t), 46.53 (t), 49.32 (t), 63.48 (d), 181.6 (s). Anal. Found: C, 64.12; H, 9.92; N, 8.76. Calc. for C₁₀H₁₃NO₂: C, 64.83; H, 10.34; N, 7.56%.

**3-Aminomethyl-3,5,5-trimethyl-cyclohexanol 5.** In a two-necked round bottom flask fitted with a reflux condenser was taken LiAlH₄ (4.92 g, 129.55 mmoles) in dry THF (300 mL) at 0°C, and 4 (6 g, 32.39 mmole) dissolved in THF (50 mL) was added to it at 0°C. The reaction mixture was refluxed for 24 hr when all the starting material was consumed. Usual work-up gave crude 5, purification of which on a silica gel column using dichloromethane and methanol solvent system in increasing proportion of polarity yielded pure yellowish liquid 5, yield 92%.
(5.10 g); IR: 3374 (for OH), 2922, 1666, 1599, 1463, 1364 cm\(^{-1}\); EIMS m/z (rel. int.): 172 [M+1]\(^+\) (5), 171 [M]\(^+\) (34); \(^1\)H NMR (400MHz, CDCl\(_3\)): \(\delta\) 0.91 (s, 3H, CH\(_3\)), 0.93 (s, 3H, CH\(_3\)), 1.36 (s, 3H, CH\(_3\)), 1.42 (m, 2H, CH\(_2\)), 1.55 (m, 2H, CH\(_2\)), 1.66 (m, 2H, CH\(_2\)), 2.27 (brs, 2H, CH\(_2\)-NH\(_2\)), 3.86 (m, 1H, CH-OH); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 23.0 (q), 28.0 (q), 35.0 (q), 32.65 (s), 37.05 (s), 44.63 (t), 47.5 (t), 49.25 (t), 57.69 (t), 65.43 (d). Anal. Found: C, 70.08; H, 12.54; N, 8.32. Calc. for C\(_{10}\)H\(_{21}\)NO: C, 70.12; H, 12.36; N, 8.18%.

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References